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Walter Reed Army Institute of Research

Behavioral Biology Branch:
Actigraphy Development

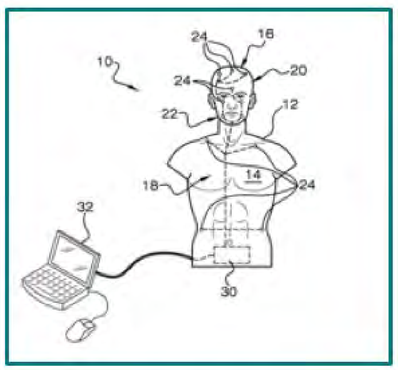
125 YEARS 1893-2018

THE PROBLEM

Soldiers suffer from insufficient sleep which negatively impacts lethality.

"One cannot manage in the field what one cannot measure in the field."
-COL Gregory Belenky

Traditional laboratory methods for monitoring sleep are impractical in the real world.



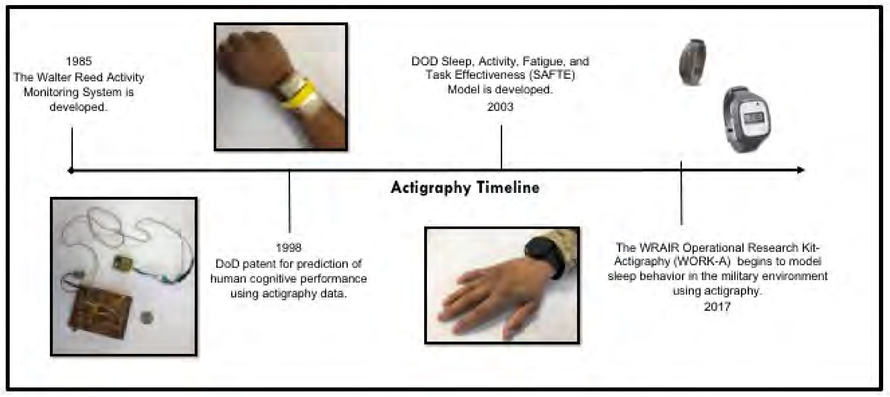
Full array polysomnography is burdensome and field-ready EEG systems are not currently optimal.

Self report of sleep can be unreliable and/or inaccurate.

OUR SOLUTIONS

Actigraphy

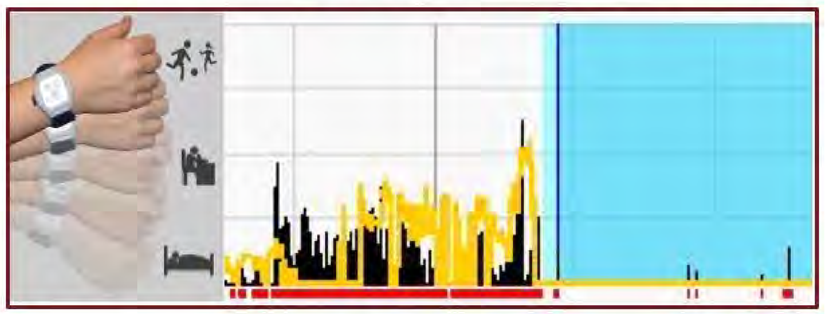
WRAIR developed a portable and unobtrusive way to measure sleep in the field.



The WRAIR Operational Research Kit-Actigraphy (WORK-A)

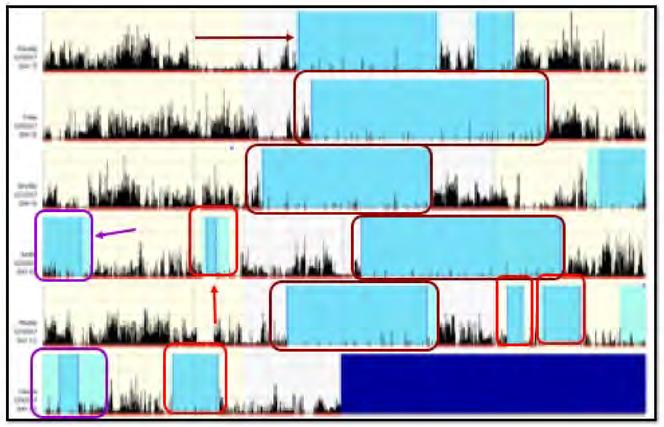
Specifically designed to measure sleep in the military operational context

Informing Models of Sleep and Fatigue



ROADMAP TO THE FUTURE

Identifying Current Issues and Areas for Improvement of Soldier Sleep Using WORK-A



Applying Strategies for Sleep Improvement

Enhancing Readiness and Lethality Through Better Sleep Quality

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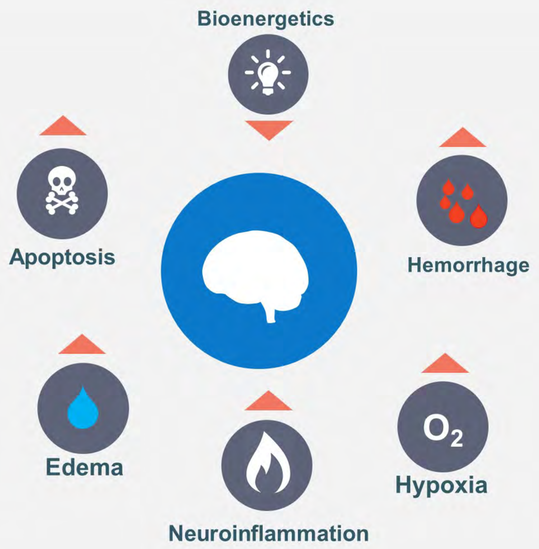
Alternative Therapies for Traumatic Brain Injury

125 YEARS 1893-2018

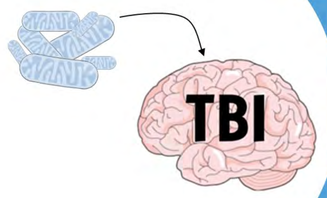
THE PROBLEM

Traumatic brain injury (TBI) is a major threat to readiness of our soldiers. They face a higher risk of TBI both in scope and frequency than civilians.



There are currently no FDA approved treatment options for TBI.

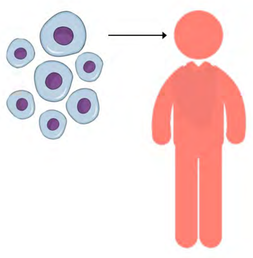
OUR SOLUTIONS



Mitochondrial Transplantation

Healthy, aspiring, allogenic mitochondria are delivered to the injured brain to improve bioenergetics.

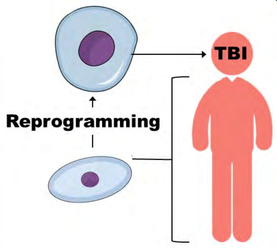
Apoptosis ↓ | Neuronal Survival & Function ↑ | Bioenergetics ↑



Human Neural Stem Cells

FDA-approved cells, which are in clinical trials for spinal cord injury and amyotrophic lateral sclerosis, are delivered to the injured brain.

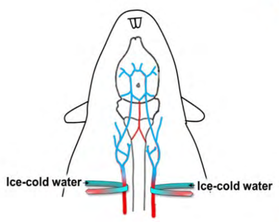
Cognition ↑ | Neuronal Population ↑ | Injury Size ↓



Directly Reprogrammed Stem Cells

Autologous cells are reprogrammed and delivered to the injury site which mitigates the immune response.
Industry Partner: Fortuna Fix

Cognition ↑ | Neuronal Population ↑ | Injury Size ↓



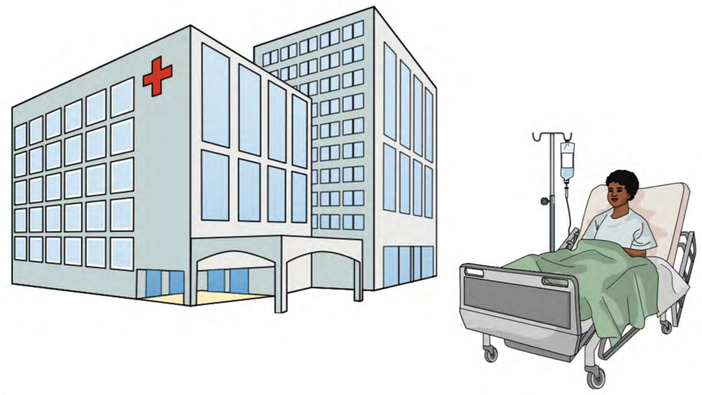
Selective Brain Cooling

Selectively cool the brain to provide neuroprotective effects, while avoiding adverse effects associated with core temperature changes.

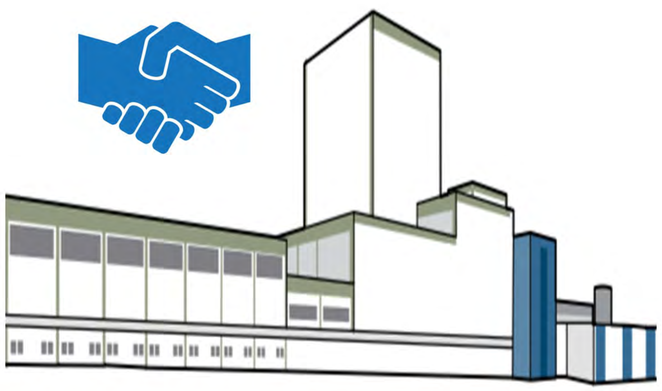
Motor Function ↑ | Edema ↓ | Intracranial Pressure ↓

ROADMAP TO THE FUTURE

1 Phase IIA Clinical Trials



2 Industry Collaborations/Development



3 Active Deployment

Research funding provided through the Combat Casualty Care Research Program

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Traumatic Brain Injury Biomarker Discovery & Development

125 YEARS 1893-2018

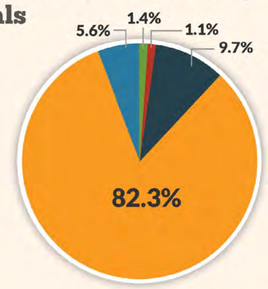
THE PROBLEM

1 Military personal are at increased risk of TBI

DoD Numbers for Traumatic Brain Injury
Worldwide – Totals

2000 - 2018 Q1

Penetrating	5,215
Severe	4,067
Moderate	37,424
Mild	315,897
Not Classifiable	21,344
Total - All Severities	**383,947**



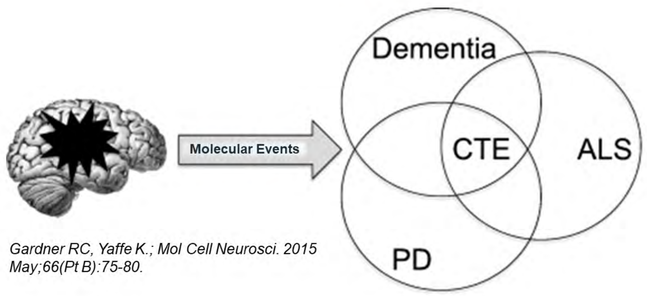
Source: Defense Medical Surveillance System (DMSS), Theater Medical Data Store (TMDS) provided by the Armed Forces Health Surveillance Center (AFHSB)

Prepared by the Defense and Veterans Brain Injury Center (DVBIC)

2000 - 2018 Q1, as of June 21, 2018

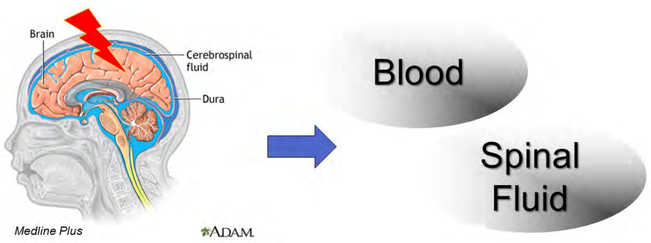
*Percentages do not add up to 100% due to rounding

2 TBI increases risk for neurodegenerative pathologies



Gardner RC, Yaffe K.; Mol Cell Neurosci. 2015 May;66(Pt B):75-80.

3 TBI Alters the Brain and Molecules Leak into Biofluids

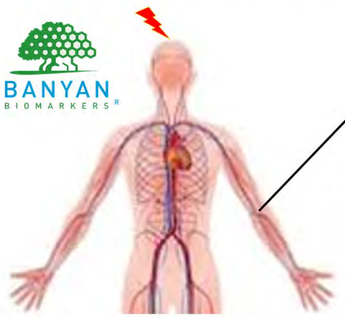


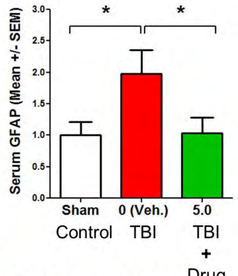
Medline Plus ADAM.

OUR SOLUTIONS

Stratify — GAUGE SEVERITY, AUGMENT CLINICAL PRACTICE GUIDELINES, TEST THERANOSTIC ABILITY

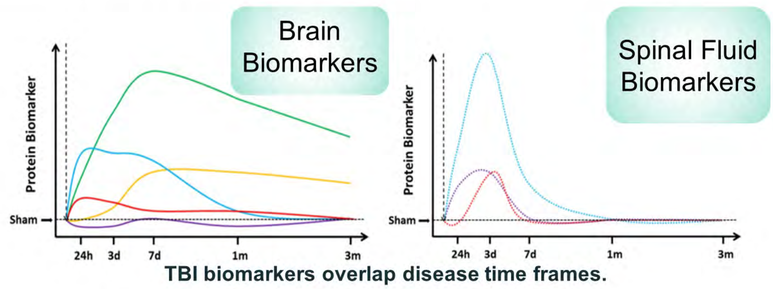
BANYAN BIOMARKERS®





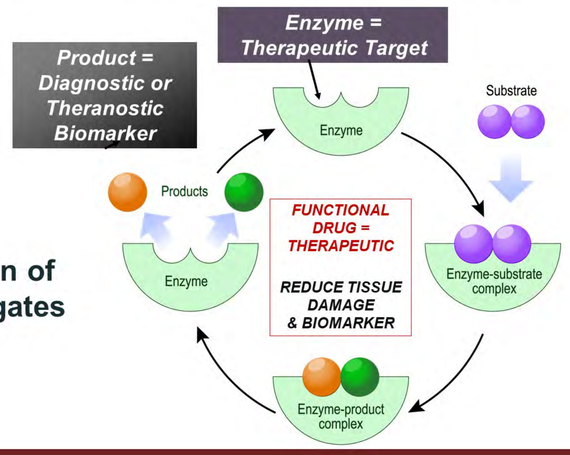
The FDA-approved blood test predicts presence/absence of intracranial lesions:
TBI + lesion = 97.5% accuracy TBI – lesion = 99.6% accuracy

Track — MONITORING OF ACUTE TO CHRONIC CNS DAMAGE AND THERAPEUTIC RESPONSES



TBI biomarkers overlap disease time frames.

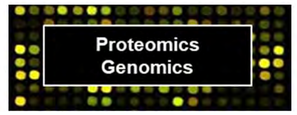
Treat — TARGET ENGAGEMENT AND FUNCTIONAL ANALYSIS FOR ENHANCED THERAPEUTIC DESIGN



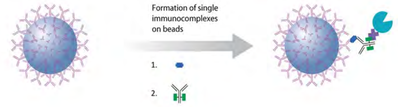
Direct inhibition of the target mitigates TBI-induced biomarkers

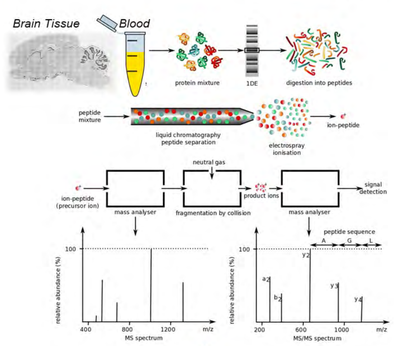
ROADMAP TO THE FUTURE

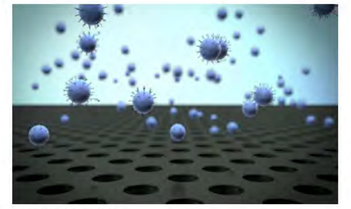
A *Discovery* → *Validation*



Thermo Scientific™ Orbitrap Fusion™ Tribrid™ MS







Courtesy of Quanterix, Inc.

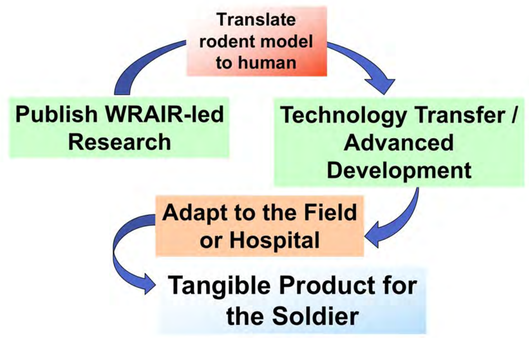
New Drug Targets & Biomarkers

Multivariate Biomarker Panels

Abbott Istat Device

Lab on a Chip (conceptual)

B *Adapt to the Field*



Research funding provided through the Combat Casualty Care Research Program

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A multi-faceted approach to characterizing the effects of repetitive low level blast (overpressure) during operational training

125 YEARS 1893-2018

The Problem

Blast exposure linked to TBI, early onset Alzheimer's/Dementia, and CTE.

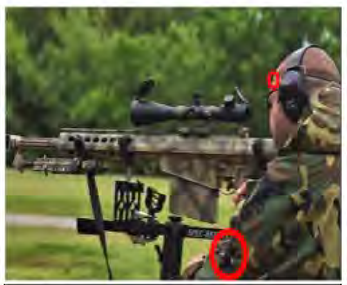
"Breachers Brain", a symptom complex identified by explosive personnel in three countries in 2008. Not identifiable as medical injury

The effects of repetitive low level blast exposure during operational training has not been quantified.

The biomechanical effects of low level blast on the brain are not known.

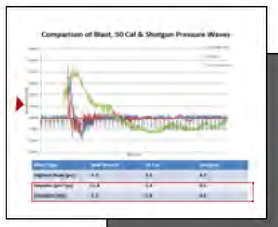
Our Solution

Quantify Overpressure exposure for different weapons systems during operational training.



50 cal. data collection and sensor position

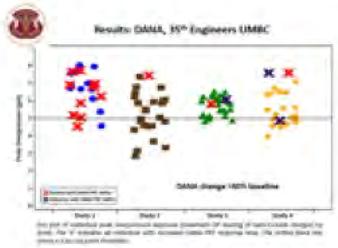
50 cal. data collection and sensor position



For the data above, similar peaks (OP) were selected. However, variation in duration lead to notable variation in cumulative impulse across platforms.

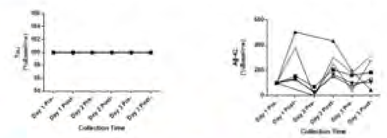
Measure Biological effects including mental performance; blood biomarkers; symptoms, etc)

Effect of blast exposure on mental performance

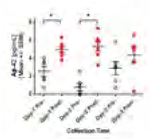


Blood Biomarkers during 3 day 50 Cal rifle training.

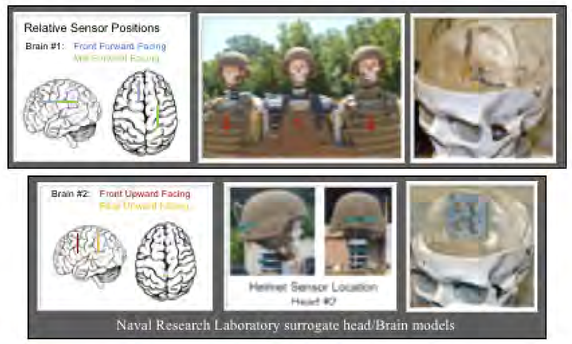
50 Cal. Exposure Preliminary Data: Serum Tau Levels Per Subject



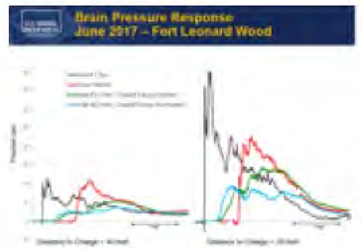
- Data derived from 5-6 of 19 subjects at Nashville, TN , Site 06, Protocol/Group 2304D Exposed to OP
- 50 cal. Exposure leads to fluctuation of amyloid beta peptides, but not tau protein in serum compared to baseline levels.
- Post-50 cal. exposure on days 1 and 2 were significant by 1-way ANOVA



Surrogates to identify effects of blast on the brain



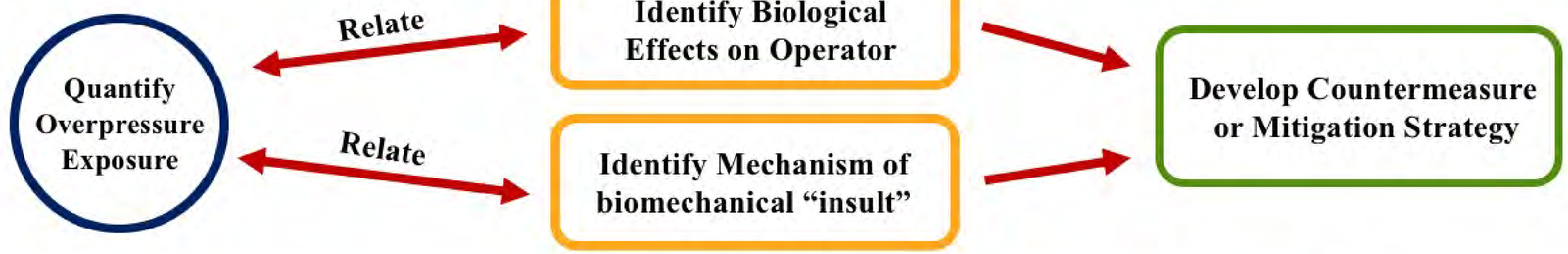
Naval Research Laboratory surrogate head/Brain models



Trace show pressure on outside of head; inside helmet and inside different brain areas.

Roadmap to the Future

Gustav Rocket Testing



Grenade Range Testing

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Cumulative Effects of Repeated Blast

125 YEARS 1893-2018

The Problem

Repeated exposures to blast overpressure in operational and training of Warfighter can lead to neurological and neurosensory deficits

Short term issues


Headache


Attention deficits


Sleep disturbances


Anxiety and Depression

Decreased soldier readiness
Compromised decision making in operation
Short term memory issues

Mid-term issues


Memory Issues


Sleep disturbances


Psychological Issues

Diminished quality of life
Cognitive decline
Substance abuse
Suicidality

Long term issues

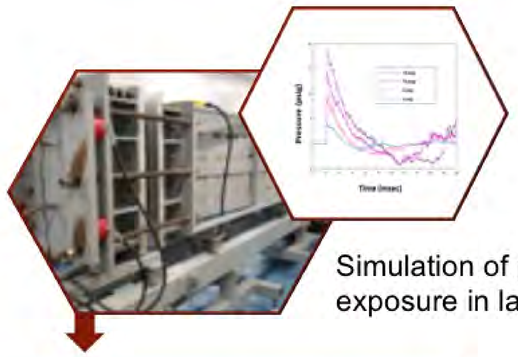

Memory Issues


Psychological Issues

All cartoon images are obtained from google

Early dementia
Suicidality
Neuropsychological issues

Our Solution



Simulation of primary blast exposure in laboratory

Repeated low level exposures to blast

Pre-clinical behavior profiling

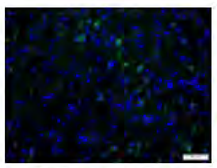

Memory test

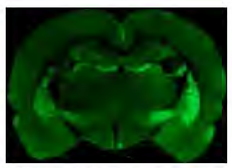

Activity


Anxiety

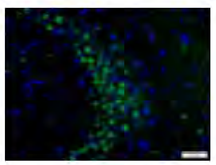

Attention/spontaneous memory

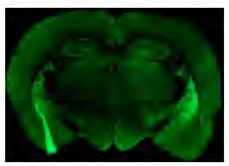
Neurodegenerative molecular changes in the brain following blast exposure

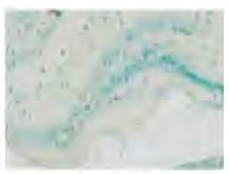

Motor cortex of rat exposed to blast


Sham rat: no blast exposure


Sham rat: no blast exposure

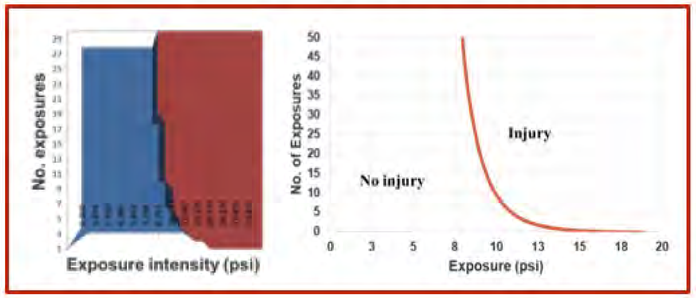

Hippocampus of rat exposed to blast


Rat exposed to blast

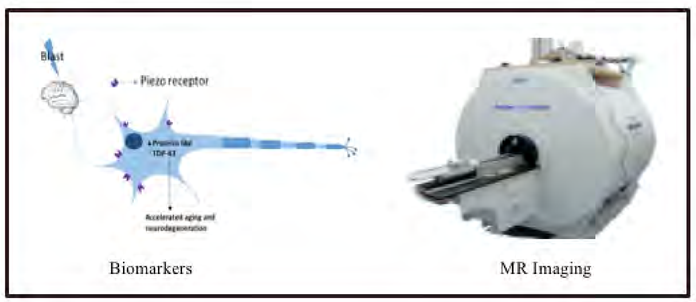

Hippocampus of rat exposed to blast

Roadmap to the Future

Algorithms to determine how much is too much



Diagnostics



Biomarkers

MR Imaging

PPE and treatment strategies


Advanced PPE

Treatment strategies

Dropout Reduction in Outpatient Psychotherapy Training

Joshua Wilk, Ph.D., Katie Nugent, Ph.D., MAJ James MacDonald, Ph.D., Kristina Clarke-Walper, MPH,
Elizabeth Penix, BA, SPC Imani Bruce, BS, & LTC Justin Curley, MD

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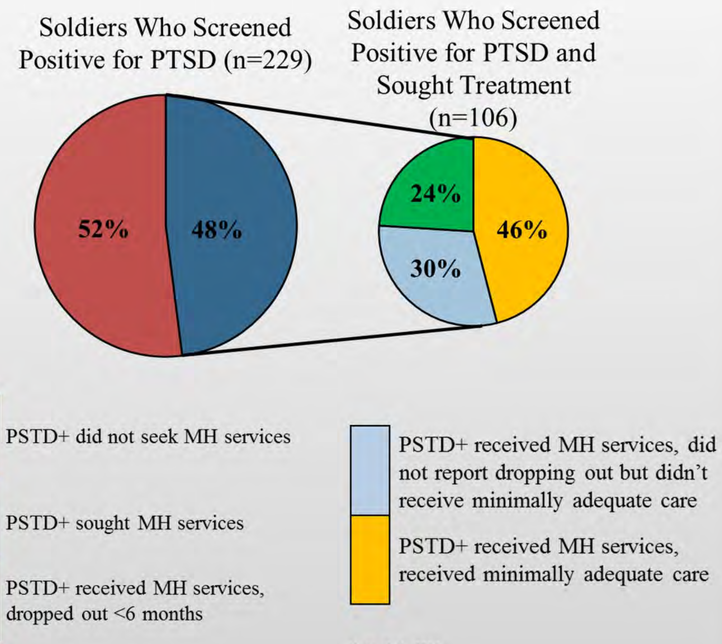
MILITARY PSYCHIATRY BRANCH • CENTER FOR MILITARY PSYCHIATRY AND NEUROSCIENCE

125 YEARS 1893-2018

The Problem

- Many soldiers end behavioral health (BH) treatment too early.
- Treatment dropout makes it more likely the soldier will still have behavioral health problems.
- One study of Soldiers with PTSD found that among those that attended treatment, 22% attended only 1 session and only 41% attended 8 or more sessions (Hoge et al., 2014).

Behavioral Health Treatment Engagement

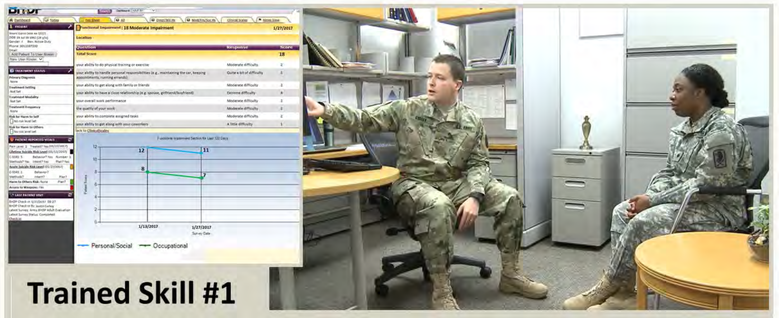


Hoge et al., 2014

Our Solution

DROP Training

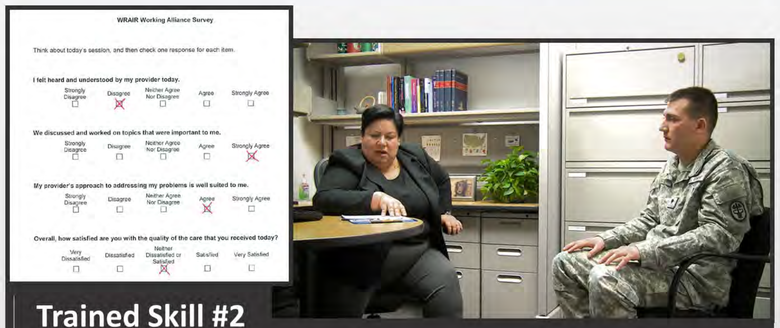
A 75-minute interactive training given to Army Behavioral Health Providers to address the problem of dropout and train two skills to prevent dropout.



Trained Skill #1

Progress Informed Treatment

Incorporating data about the patient's symptoms and functioning into the session (i.e. reviewing surveys, showing graphs of change).



Trained Skill #2

Assessment and Discussion of the Therapeutic Alliance

Asking the patient to complete a survey about the relationship with the provider during the session, then discussing the scores.

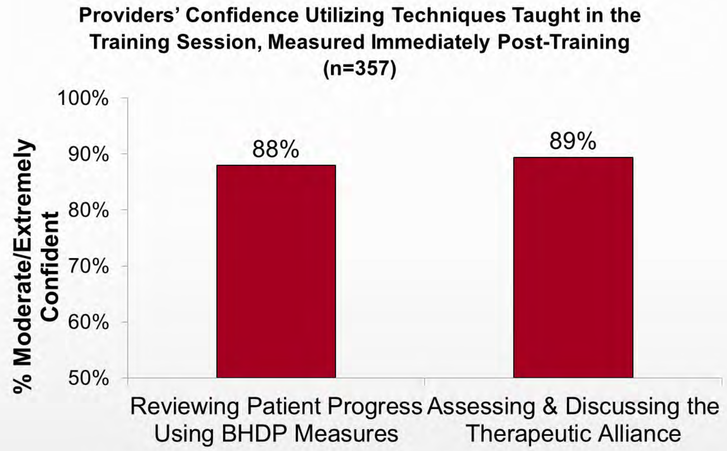
Study Design & Outcomes

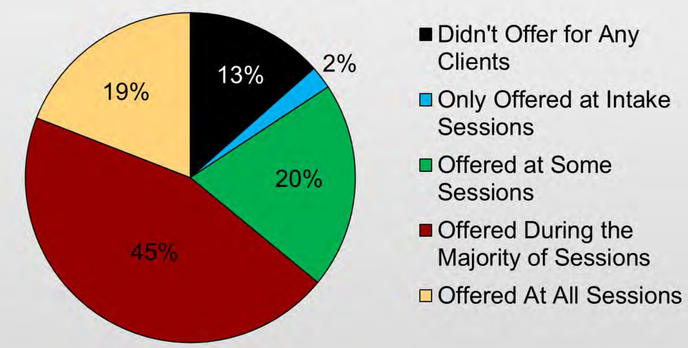
- 622 providers attended the training across 15 sites.
- Training effectiveness (e.g. change in dropout rates and treatment satisfaction scores) evaluated using a pre/post-test design using data from existing Army data sources.

Roadmap to the Future

Partnering with the Behavioral Health Service Line of the OTSG to analyze data on training effectiveness and integrate the training into Army-wide training initiatives.

Initial Results





This study was conducted with core funding from the U.S. Army Medical Research and Materiel Command's Psychological Health and Resilience research area.

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Behavioral Biology Branch Mission:

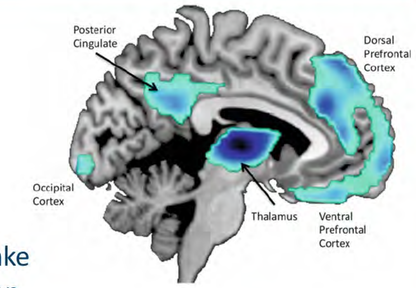
Fatigue Management for Military Operations

125 YEARS 1893-2018

THE PROBLEM

Sleep loss reduces military performance

Sleep loss impairs:
×Judgment
×Awareness
×Problem solving
×Creativity
×Reaction time
×Attention



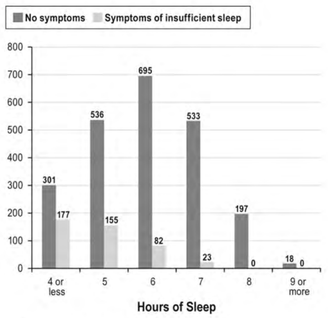
These abilities can make the difference between mission **success** and **failure**

Sleep loss reduces Soldier health & resilience

Millennium Cohort Study:

- ~51% of Soldiers get less than the recommended 7-9 hours of sleep.
- Short sleep is associated with poor subjective health, increase in doctor visits, more lost work days, lower likelihood of deployment, and early separation from the Military (Seelig et al., 2016).

Sleep loss is common in the military operational environment



(Luxton et al., 2011)

- In one study, ~72% of Soldiers got less than 7 hours of sleep per night
- ~43% experienced severe chronic sleep restriction – averaging 5 or less hours of sleep per night

OUR SOLUTIONS

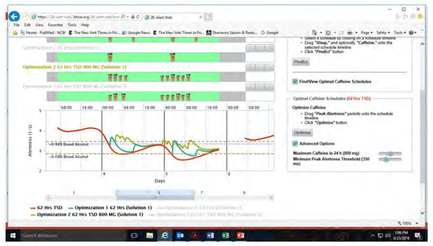
WS^3

WRAIR Soldier Sustainment System

1 Hardware: wrist actigraphy

Well-validated way to objectively measure and record timing & duration of sleep in operational environments.

2 Software: 2b-alert prediction model

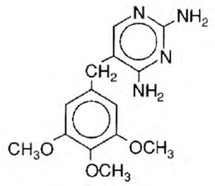


(Reifman et al., 2018)

- Mathematical performance prediction model developed by BHSAI and WRAIR
- Predicts performance based on sleep/wake history and the circadian rhythms
- Recommends how to optimize performance with caffeine

3 Interventions: sleep inducers & stimulants

Sleep inducers, like Ambien, restore sleep under non-sleep conducive conditions



+

Stimulants, like caffeine, sustain alertness and performance when adequate sleep is not possible

ROADMAP TO THE FUTURE

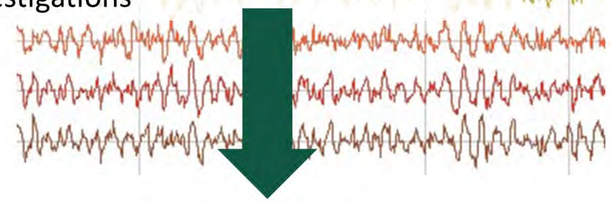
Goal 1: A biomarker for resilience to sleep loss

The ability to tolerate sleep loss varies greatly across individuals. It is thought that these individual differences are mediated by genetics (e.g., PER3 and ADORA 2A SNPs) and/or levels of long-term sleep debt.

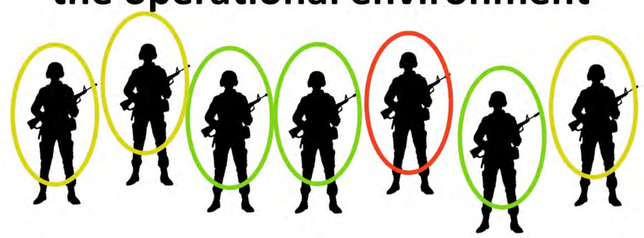
+

Goal 2: A sleep debt biomarker

- Provides a baseline to predict performance with the 2B-Alert app
- Determines'fitness for duty' (or driving, operating machinery, etc.) in real time
- Invaluable for post-hoc accident investigations



Ultimate Goal: Control fatigue in the operational environment



Sleep Debt + Individualized Resilience = Fatigue Management

References

1. Seelig AD et al., (2016). Sleep and Health Resilience Metrics in a Large Military Cohort. *Sleep*, 39(5):1111-20.
2. Luxton DD et al., (2011). Prevalence and impact of short sleep duration in redeployed OIF soldiers. *Sleep*, 34(9):1189-95.
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Cognitive Mechanisms of Health and Performance

Phillip J. Quartana, Ph.D., CPT Jeffrey M. Osgood, Ph.D., Morgan Conway, Ph.D.
Walter Reed Army Institute of Research, Center for Military Psychiatry and Neuroscience

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Walter Reed Army Institute of Research

125 YEARS 1893-2018

The Problem

Psychological and behavioral health problems are prevalent in the US Army, and represent a leading cause for evacuation and barrier to force readiness and lethality.

Our Solution

Targeted Solution: Cognitive Bias Assessment and Manipulation

THREAT FACE INTENSITY GRADIENT

We utilize standardized word and pictorial databases to assess and manipulate various aspects of cognitive processes that dually underlie health and readiness, with a specific emergent focus on mechanisms of optimized lethality (e.g., simulated marksmanship performance).

Optimized Affect Discrimination in domains of Threat, Fear, and Positivity → ↓ **Lethal Force Decision Making**

↑ **Operational and Combat Stress Symptoms**

Roadmap to the Future

- Cognitive bias assessment and modification integration with smart phone application technology
- Integrate with tools available for neural fortification (e.g., tDCS)

Hostile Interpretation Bias Mitigation Training → ↓ **Anger, aggression, and hostility**

LINKS: An Evidence-Based Intervention Targeting Behavioral Health Treatment-Seeking

WRAIR Walter Reed Army Institute of Research

125 YEARS 1893-2018

The Problem

4 out of 5

Soldiers who **have a behavioral health** concern are **not currently in treatment**

(Colpe et al., 2015)

support from peers and leaders may boost behavioral health care utilization

increases **positive perceptions** of BH treatment

increases **willingness to challenge BH stigma**

increases **supportive behaviors** toward Soldiers with BH problems

(Britt et al., 2018)

Creating a Supportive Climate for Soldiers who Need Help Training

funded by the Army, Dr. Thomas Britt and colleagues from Clemson University developed a 2-hour training for units and leaders

1. is the Britt supportive climate training effective in an operational setting when delivered by Army trainers?
2. can the training be effectively trained in one hour instead of two?

Our Solution

the RTO created "LINKS", an adaptation of the Britt supportive climate training

links

purpose: improve unit support for behavioral health treatment-seeking

look for signs (l)	increase awareness (i)	neutralize barriers (n)	know your role (k)	support help seeking (s)
separate trainings for the unit and its leaders	discussion- and exercise-based	video interviews with treatment seekers		

Effectiveness Evaluation

an evaluation was conducted to assess the effectiveness of the 2-hour module against an abbreviated, 1-hour version of the LINKS curriculum relative to comparable (2-hour and 1-hour) active control groups

each training was delivered to two platoons, for a total of eight platoons

surveys (at pre-training, post-training, and 3-month follow-up) were used to evaluate training effectiveness

well received by Soldiers — USEFUL

improved behavioral health **knowledge**

at post-test and 3M follow-up

reduced attitude barriers toward treatment

at post-test and 3M follow-up

2H

effects generally greater for 2-hour module

Roadmap to the Future

the LINKS evaluation is a prototype for effectiveness studies conducted by the RTO in conjunction with Army stakeholders *

Dissemination

stakeholder dissemination

1. findings from the LINKS effectiveness evaluation were briefed to unit leadership and stakeholders at the Army Resiliency Directorate (ARD) and the Army Office of the Surgeon General (OTSG)

scientific dissemination

2. findings from the LINKS effectiveness evaluation will also be delivered to the scientific community through conference presentations (e.g., the 2018 Military Health System Research Symposium [MHSRS]) and peer-reviewed publications

3. in FY18, the full LINKS curriculum was delivered to the **Army Resiliency Directorate (ARD)** for inclusion on their resilience training menu

2H

Implementation

optimal benefits will result from delivery of the 2-hour LINKS module with periodic refresher sessions

the **Pulse** (formerly the Unit Behavioral Health Needs Assessment) can be used to identify units that might want to prioritize LINKS training

References

Britt, T.W., Black, K.J., Cheung, J.H., Pury, C.L.S., & Zinzow, H.M. (2018). Unit training to increase support for military personnel with mental health problems. *Work & Stress, 32*(3), 281-296.

Colpe, L.J., Naifeh, J.A., Aliaga, P.A., Sampson, N.A., Heeringa, S.G., Stein, M.B., . . . & Kessler, R.C. (2015). Mental health treatment among soldiers with current mental disorders in the Army Study to Assess Risk and Resilience in Service Members (Army STARRS). *Military Medicine, 180*(10), 1041-1051.

MedFit:
Resilience Training for Healthcare Staff

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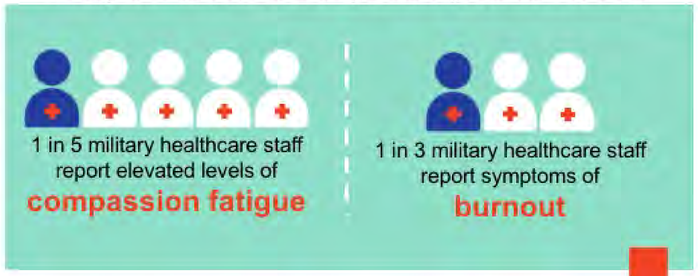
125 YEARS 1893-2018

The Problem

military healthcare staff face unique challenges to their resilience



(Adler et al., 2017; Sinsky et al., 2013)

compassion fatigue and burnout negatively impact healthcare staff well-being, the care provided to patients, and employee turnover in the Military Health System.

self-care can help reduce compassion fatigue and burnout

Our Solution

MEDfit+

purpose:
to equip healthcare staff with self-assessment and self-care skills to (1) prevent compassion fatigue and burnout and (2) achieve and maintain optimal functioning

Outcomes Evaluation

1. does MedFit effectively reduce compassion fatigue and burnout?
2. is a 1-hour module as effective as the 2-hour?

an evaluation is currently in progress to assess the effects of MedFit on healthcare staff well-being

staff at two military treatment facilities are being randomly assigned to the 2-hour module, the 1-hour module, or the waitlist control

surveys (at pre-training, post-training, and 3-month follow-up) are being used to evaluate training outcomes

Roadmap to the Future

1. complete the outcomes evaluation and provide implementation recommendations for the MedFit curriculum to the Army Office of the Surgeon General

* **MedFit is a prototype for targeted resilience training products developed by the RTO**

targeted products recognize that certain subgroups within the Army face unique challenges to their resilience and need resilience skills tailored to their context

2. continue identifying subgroups of Soldiers and developing targeted products

for example

military veterinary staff also face unique challenges to their resilience

(McLeod, Sikka, Hill, Wilson, & Pecko, 2017)

VETfit

VetFit will adapt the existing MedFit curriculum and integrate evidence-informed content to address veterinary-specific topics such as social support

References

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McLeod, V., Sikka, R., Hill, C., Wilson, A., & Pecko, J.A. (2017). Assessment of behavioral and occupational health within the U.S. Army Veterinary Services, April – June 2017. Technical Report No. WS.0049403.

Mindfulness: An Emerging Strategy for Enhancing Health and Readiness

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Walter Reed Army Institute of Research

The Problem

combat exposure can negatively impact behavioral health

stress can deplete key mental resources that Soldiers need to perform optimally

mindfulness can help mitigate the harmful effects of combat exposure and stress

lower depression, anxiety, PTSD, perceived stress

less aggression, risk-taking, and alcohol misuse

better emotional regulation and adaptation to stress — emotions

protected working memory and attention during computer-based tests

(Jha et al., 2010)

mindfulness awareness of the present moment without elaboration, judgment, or emotional reactivity

mindfulness is linked with **better behavioral health** and **cognitive performance** in lab-based tests

1. does mindfulness protect Soldiers who experience high levels of combat?
2. can mindfulness improve operational outcomes?
3. do Soldiers benefit from practicing mindfulness during the duty day?

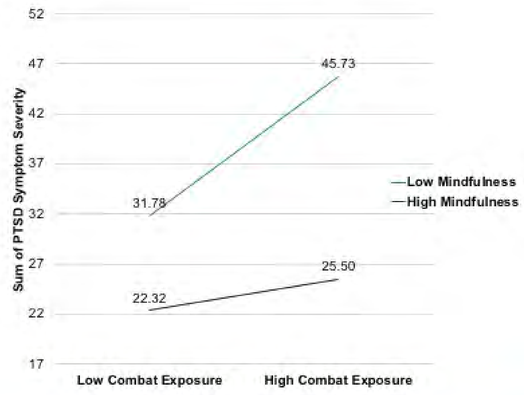
Our Solution

1 establish protective nature of mindfulness under high levels of combat

627 Soldiers returning from a combat deployment were surveyed at two time points

mindfulness buffered against subsequent deployment health problems, including PTSD, depression, and pain symptoms

(Nassif et al., in press)



Mindfulness Operational Outcomes Study

evaluate impact of Mindfulness-Based Attention Training (MBAT) on health and performance under stress

2 assess impact of mindfulness on operational outcomes

- accuracy
- decision-making
- working memory
- target discrimination
- attention
- communication
- endurance

3 determine benefit of mindfulness practice being integrated into the duty day

Roadmap to the Future

1 develop best practices for delivering mindfulness training to Soldiers

stakeholder dissemination

2 deliver findings to the Army Resiliency Directorate to inform decisions about the use of mindfulness training Army-wide

READY AND RESILIENT

scientific dissemination

3 deliver findings to the scientific community through conference presentations and peer-reviewed publications

4 expand study of mindfulness for other operational outcomes

- engineers
- military intelligence
- General Officer readiness (in conjunction with US Army War College)

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Neurosensory Effects of Blast Wave Exposure

125 YEARS 1893-2018

The Problem

Exposures to blast overpressure waves in Warfighters can lead to damage to neurons within sensory organs, e.g. the eye and inner ear as well as related visual and auditory centers of the brain. Of blast induced ocular trauma patients, 43% display closed-eye injuries with 26% retina involvement and thus vision loss. Likewise, for blast victims with ear trauma, 49% display conductive hearing loss and 76% develop tinnitus. There are no approved therapeutic interventions for these afflictions.

BLAST OVER PRESSURE WAVE

HUMAN EYE ANATOMY

HUMAN EAR ANATOMY

Training and Operational exposures can lead to neurosensory injuries with debilitating effects

Short/Mid term deficits

Visual function losses

Accommodation

Photophobia

Saccades

Auditory function losses

Temporary and permanent threshold shift of heating

Vertigo & balance

Tinnitus and visual impediment
Decreased soldier readiness
Compromised environmental cue input
Operational compromise

Long term deficits

Blindness

Deafness

Psychological issues

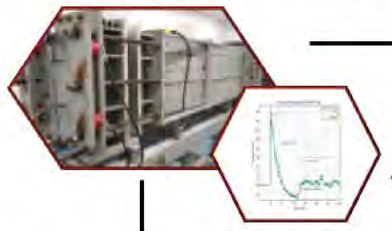
Diminished quality of life
Increased accident risk
Substance abuse
Suicidality

Our Solution

In a rat model of simulated blast over pressure wave exposure characterize damage to the neurons comprising the retina and cochlea (e.g. photoreceptors and hair cells, respectively), using assessments of pathophysiological changes. Apply this knowledge to identify the underpinning injury mechanisms as targets and then evaluate related therapeutics interventions to prevent blast-induced vision and hearing loss. Our deliverable is animal testing data for the advancement of human clinical trials.

Preclinical model of blast overpressure

Advanced blast simulator and overpressure waveform



Magnetic Resonance Imaging (MRI) based ocular macrophage cell tracking

Audiogram

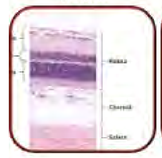
Functional assessments

Electroretinogram (ERG) of retina

Auditory brainstem (ABR) of inner ear

Histopathology assessments

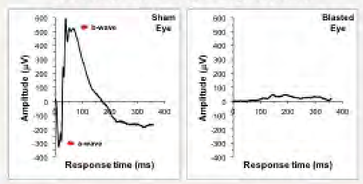
Retina



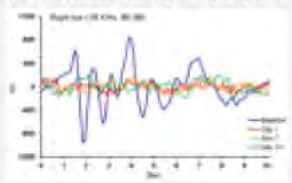
Cochlea

Functional deficits following blast exposure

Decreased retina signaling response

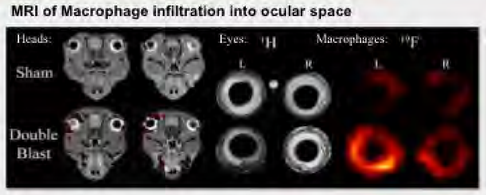


Decreased inner ear signaling response

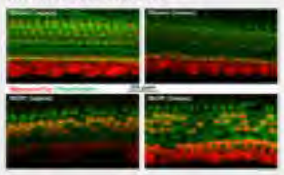


Pathophysiological following blast exposure

MRI of Macrophage infiltration into ocular space

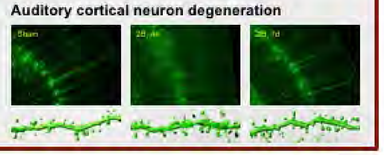


Cochlear hair cell loss



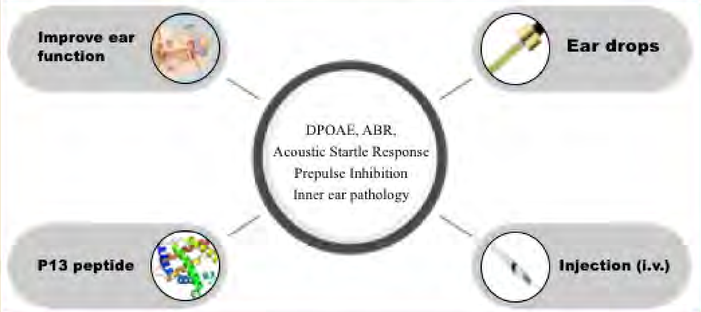
Damage to eye structures

Auditory cortical neuron degeneration

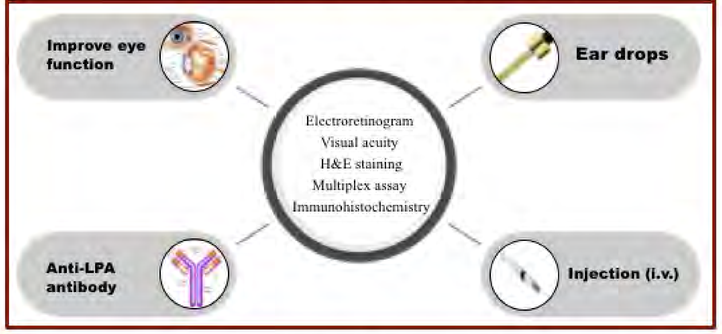


Roadmap to the Future

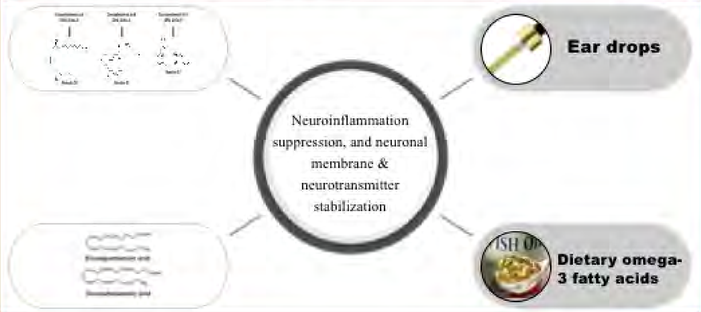
Anti-inflammatory peptide therapy against auditory dysfunctions



Antibody therapy against ocular dysfunctions



Nutritional interventions and drug delivery platforms against blast



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Wang Y, et al. Dendritic structural plasticity may contribute to blast exposure-induced auditory dysfunction in mice. Joint Symposium of The International and National Neurotrauma Societies and AANS/CNS Section on Neurotrauma and Critical Care 2018; Toronto, Canada;

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Performance Assessment and Chemical Evaluation (PACE) Laboratory

125 YEARS 1893-2018

THE PROBLEM

Acute trauma exposure disrupts performance and reduces Service Member readiness.

Mental health concerns are the **#1 reason for medical evacuations** out of deployed settings.

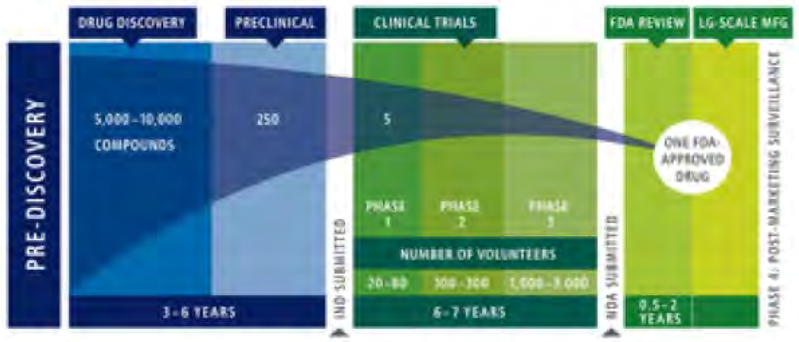
Up to **1 in 4 ServiceMembers** exposed to psychological trauma during deployment develop PTSD.

Many more develop **acute stress disorder,** though the actual number is unknown.

Current treatments for traumatic stress have limited efficacy, especially for Service Members.

OUR SOLUTIONS

Develop new pharmacological treatments for traumatic stress using a state-of-the-art 3-step process.



1 Identify and test novel compounds for efficacy using a preclinical screen.

2 Advance candidate compounds for GLP safety testing.

3 Test candidate compounds in first-in-human clinical trials.

ROADMAP TO THE FUTURE

Submit successful compounds for FDA **approval as first-line treatments.**

Incorporate successful compounds in to **behavioral health treatment guidelines and provider toolkits.**

Applications of successful compounds in far forward settings will be explored.

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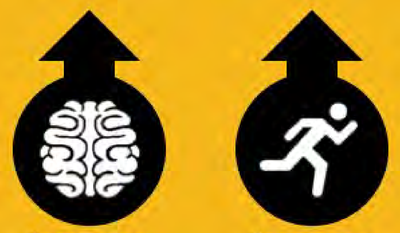
Resilience and performance: Evaluating coaching in the field

125 YEARS 1893-2018

The Problem

The Army uses mental skills training to enhance Soldier readiness



increases **resilience**

increases **performance**

Mental skills can be taught…

Formally
in a classroom

Informally
during everyday activities

Formal classroom teaching can be efficient for some tasks but…

- requires dedicated time on a training calendar
- may be harder to engage Soldiers and to make concepts "stick" when taught out of context
- may be rushed and taught below standard due to time restraints and complexity*

Our Solution

Work with stakeholders to assess a new "coaching" model

Cadet Summer Training 1

Evaluate mental skills coaching by embedded Performance Experts

Participants:
~6,000 Cadets
40 Performance Experts

Measures:
Operational performance scores (rifle marksmanship, land navigation, etc.)

MRT Coach 2

Evaluate mental skills coaching by Master Resilience Trainers (MRTs)

Current approach:
Prepare "*trainers*" use PowerPoint slides in formal classroom settings

New approach:
Prepare *"coaches"* to demonstrate and reinforce skills directly at the point of application

Roadmap to the Future

Cadet Summer Training | **MRT Coach**

Identify and develop best practices for coaching mental skills with Soldiers

Brief results to the Army Resiliency Directorate to inform implementation of mental skills coaching model

READY AND RESILIENT

*WRAIR implementation evaluation of MRT program, 2013

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SLEEP TO PERFORM:
New Advancements and Technologies for the Warfighter

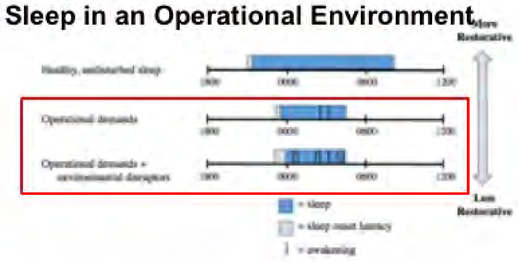
125 YEARS 1893-2018

THE PROBLEM

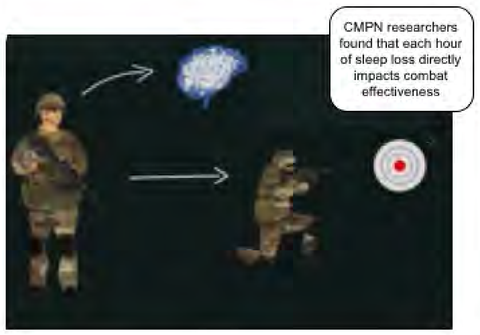
Soldiers aren't sleeping enough.

LOSS OF SLEEP= LOSS OF PERFORMANCE

Sleep in an Operational Environment

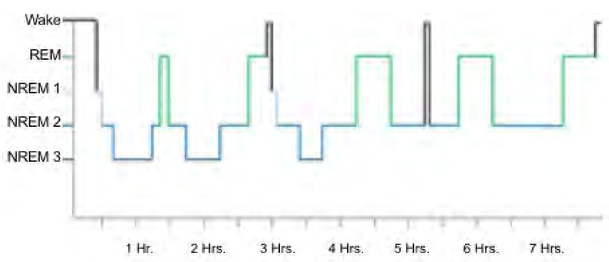


SRC researchers found that Soldiers get less than six hours a day and sleep in multiple bouts



CMPN researchers found that each hour of sleep loss directly impacts combat effectiveness

A cycle through all stages of sleep is 90 minutes. Repeated cycling over a night of sleep is essential for **recovery** and **readiness**.



Functions of REM Sleep

- Emotion Regulation
- Memory Consolidation
- Information Integration
- Dreaming

Functions of NREM Sleep

- Energy Restoration
- Memory Consolidation
- Muscle Recovery
- Toxin Clearance

PRIORITIZE SLEEP!
It reduces **fatigue** and **burnout**, and enhances **productivity** and **safety**

OUR SOLUTIONS

Develop new interventions to overcome fatigue and enhance performance

Caffeine gum

Caffeine gum developed by the CMPN provides a fast-acting solution to readiness

2B-Alert Smartphone app

- Not all individuals need caffeine to perform optimally. Too much caffeine can negatively impact readiness.
- 82% of Soldiers use caffeine regularly without guidance

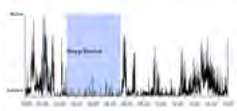
- Individualized caffeine dosing schedule provided by Smartphone app as a result of SRC studies

RESULT: All individuals perform optimally during critical times

Human Genome

SRC researchers have analyzed segments of the human genome to help identify individuals resilient to sleep loss and sensitive to caffeine

Enhancing slow wave sleep with electrical & acoustic stimulation



TELEDYNE SCIENTIFIC & IMAGING

New research suggests using non-invasive electrical and acoustic stimulation can enhance the most restorative aspect of sleep (i.e. slow wave sleep)

RESULT: Make limited sleep opportunities more restorative

ROADMAP TO THE FUTURE

Discover new pathways and identify new drug targets and technologies

From the Lab

- Performance Modeling
- Sleep physiology in the Warfighter

Monitor

To the Warfighter

Prevent **Reverse**

Interventions tested in the lab and transitioned to the field

References

Doty TJ et al (2017). Limited efficacy of caffeine and recovery costs during and following 5 days of chronic sleep restriction. *Sleep* 40(12).

Brager et al (2018). Associations of genetic polymorphisms of sleep resiliency, intensity, morning preference, and caffeine sensitivity with neurobehavioral performance under repeated cycles of total sleep deprivation. *Sleep* 41(Suppl).

Skeiky et al (2018). Self-reported sleep, actigraphy, and mental health during pre-mission qualification training in the military. *Sleep* 41(Suppl).

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Soldier And Family Behavioral Health And Readiness

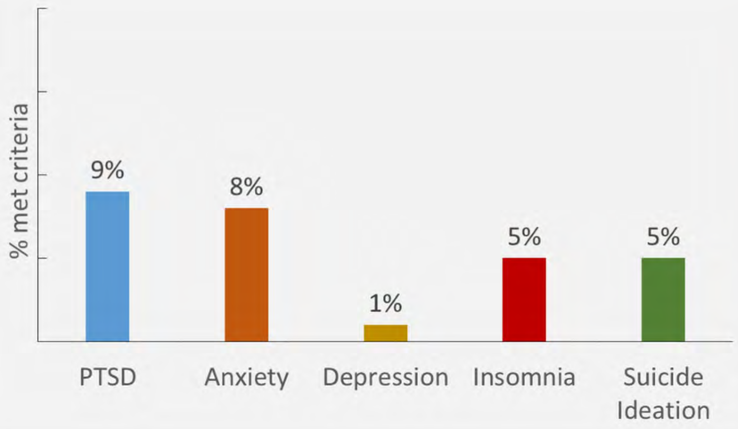
125 YEARS 1893-2018

MILITARY PSYCHIATRY BRANCH • CENTER FOR MILITARY PSYCHIATRY AND NEUROSCIENCE

The Problem

Identify Soldier behavioral health concerns and health risk behaviors

BEHAVIORAL HEALTH SNAPSHOT OF A UNIT



Our Solution

➤ **Field cross-sectional & longitudinal surveys with operational units**

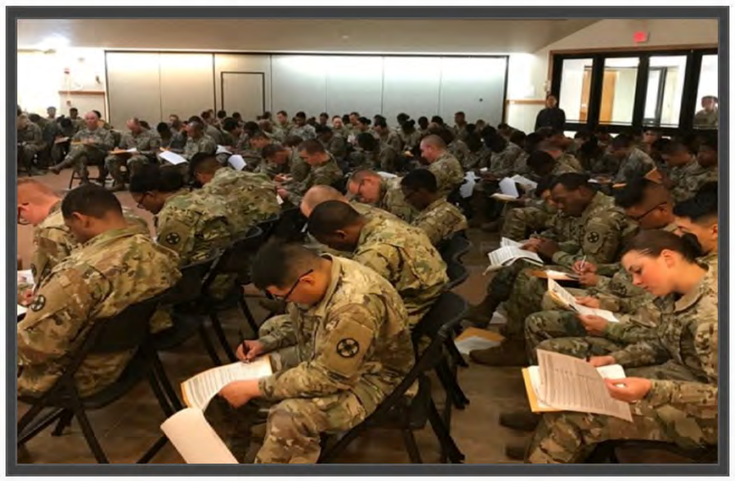
Mental Health Advisory Teams (MHATs)

➤ **Focus groups**

Security Forces Assistance Brigades

BH Pulse

Roadmap to the Future



Future Assessments:

Explore the use of mobile phones and tablets

Assessments of other SFABs

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Traumatic Brain Injury
Battlefield Point of Injury Care

125 YEARS 1893-2018

THE PROBLEM

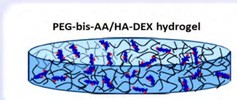
There is no FDA approved therapy for traumatic brain injury (TBI). Severe TBI currently accounts for 20% of all Joint Theater Trauma Registry (JTTR) reviewed combat casualties and, *second only to hemorrhage, severe penetrating TBI represents our most significant debilitating and life-threatening trauma.*

Military planning for future multi-domain battlefields project higher numbers of trauma casualties with greater injury severities in an environment where direct support or medical evacuation may not be available extended periods of time.

The Combat Casualty Care Research Program (CCCRP) has challenged us to develop novel and ground-breaking solutions to TBI, which can be readily employed at the point-of-injury, to mitigate morbidity and mortality in a prolonged field care environment.

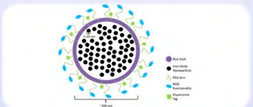
OUR SOLUTIONS

Hydrogel-Embedded Drug Delivery



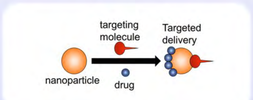
A biodegradable hydrogel scaffold that is capable of sealing the wounded environment and facilitating the controlled, continuous release of potent anti-inflammatory and antibiotic drugs directly to the injured brain. Collaboration with Dr. Jeoungsoo Lee and Dr. Ken Webb, Clemson University Department of Bioengineering

Magnetic Hemostatic Nanoparticles



A novel hemostatic, magnetic nanoparticle capable of accelerating blood clot formation in targeted areas to mitigate intracerebral hemorrhage from severe TBI. Collaboration/CRADA with Luna Nanotech Inc., Toronto, ON, CN.

Targeted Nanoparticle Drug Delivery



Novel nanoparticles designed to deliver drugs directly to neurons or glial cells in order to improve therapeutic efficacy and reduce adverse effects. Collaboration with Dr. Michael Sailor and Dr. Ester Kwon, University of California, Department of Bioengineering

Operation Brain Trauma Therapy (OBTT) is a multi-center consortium evaluating the most promising therapies across TBI animal models. This consortium is critically important to ensure reproducibility and validity in preclinical testing so that we can move at the speed of relevance while de-risking research efforts for the Army.

OBTT Operation Brain Trauma Therapy

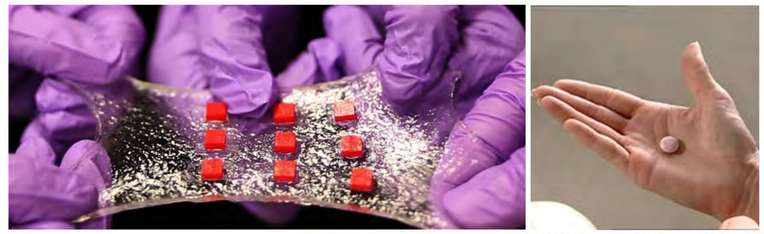
Primary Research Sites:

1. **University of Pittsburgh**
   - *Dr. Patrick Kochanek, OBTT PI*
   - *Dr. Edward Dixon, CCI model*
2. **Miami Medical University**
   - *Dr. Dalton Dietrich*
   - *Dr. Helen Bramlett, FPI model*
3. **Walter Reed Army Institute of Research**
   - *Dr. Deborah Shear, PBBI model*
   - *Dr. Joseph Long, Blast TBI model*
4. **Virginia Commonwealth University**
   - *Dr. John Povlishock*
   - *Dr. Audrey LaFrenaye, Pig TBI model*
5. **Biomarker Core**
   - *Dr. Ronald Hayes, Banyan Biomarkers*
   - *Dr. Kevin Wang, University of South Florida*
   - *Dr. Stefania Mondello, Messina University*

ROADMAP TO THE FUTURE

ACT!

Use Adaptive Clinical Trial Design and DoD/Army sponsored TRACK TBI NET to rapidly advance the most promising therapies into clinical testing.



Research funding provided through the Combat Casualty Care Research Program

US Army Medical Research and Materiel Command
CCCRP
COMBAT CASUALTY CARE RESEARCH PROGRAM

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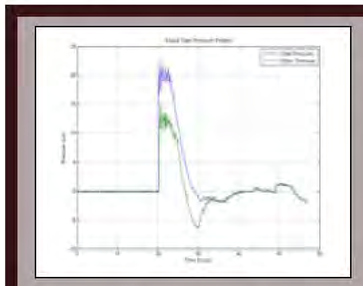
The Physics and Biomechanical Study of Blast

125 YEARS 1893-2018

The Problem

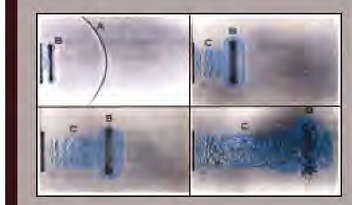
A poor understanding of blast physics by the biomedical research community has resulted in inappropriate blast exposure and in turn led to erroneous results and incorrect conclusions.

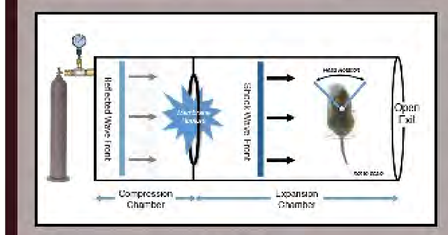
Cylindrical shock tube in use at WRAIR until 2013 produced shock waves with artefactually high winds (>400 mph).



Pressure recordings from the shock tube shown above. Notice the long positive pressure phase (~10msec) and the plateaued peak pressure.

Item under test placed at the end of a shock tube will be exposed to end-jet effects (shown below) not seen in actual explosions.



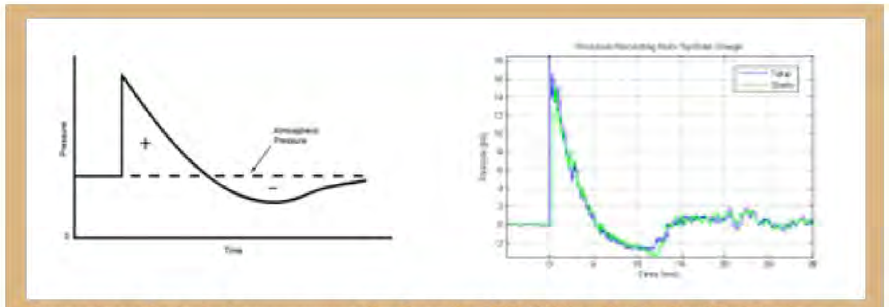


Unsecured animal head will be exposed to significant artefactual blast wind as well as rarefaction waves from open end.

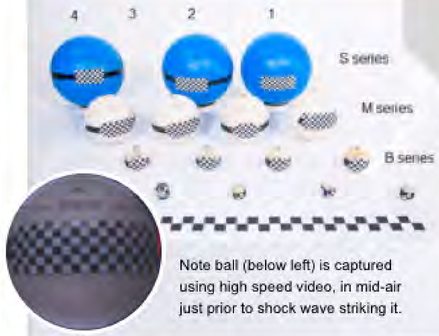
Our Solution

In partnership with world-renowned blast physicist, Dave Ritzel, BINT has procured an Advanced Blast Simulator (ABS) capable of producing consistent high fidelity blast waves.

The Advanced Blast Simulator, showing, from left to right, the driver section, the unique divergent transition section, the test section and the end-wave eliminator.

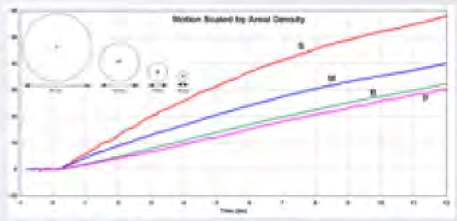


Comparison of a typical pressure recording from the ABS (right) to the idealized Freidlander wave



Note ball (below left) is captured using high speed video, in mid-air just prior to shock wave striking it.

Experiments with a series of weighted spheres of different sizes (shown left) has lead to important insights into scaling.

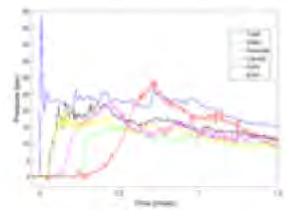


Roadmap to the Future

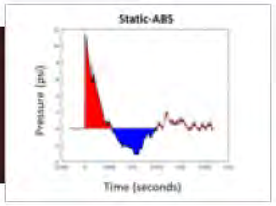
Collaborative studies using high fidelity blast simulations to promote advances in personal protective equipment (PPE), computational modeling for risk assessment, complex polytrauma and inform scaling across species.

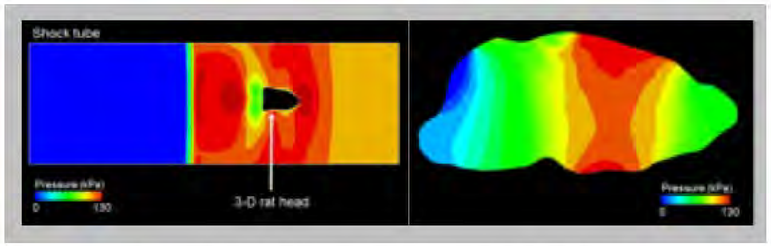
Developing blast overpressure exposure standards for PPE.

Simultaneous pressure measurements (right) during blast using Millar catheters. Note two ICP placements: epidural and ventricular. From an on-going collaboration with the Institute of Nuclear Medicine and Allied Sciences, New Delhi, India.



Relating impulse measurement to injury in a joint project with NMRC





Computational modeling of blast overpressure on the brain of a rat.
From an ongoing collaboration with the Naval Medical Research Unit-San Antonio (NMRU-SA)

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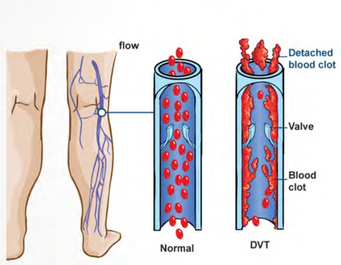
Translating Preclinical Research into Clinical Practice Guidelines for the Acute Management of TBI

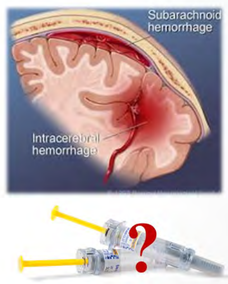
125 YEARS 1893-2018

THE PROBLEM

Hemorrhage is the leading cause of combat casualty and often occurs in conjunction with traumatic brain injury (TBI). *There is controversy whether current resuscitation and treatment strategies for extremity trauma are safe for use in TBI patients.* Resuscitative endovascular balloon occlusion of the aorta (REBOA) for non-compressible hemorrhage, various pre-hospital resuscitation strategies, and the prophylactic use of heparinoids for mitigating deep vein thrombosis, all represent standards of care for trauma patients that may be contraindicated for TBI.

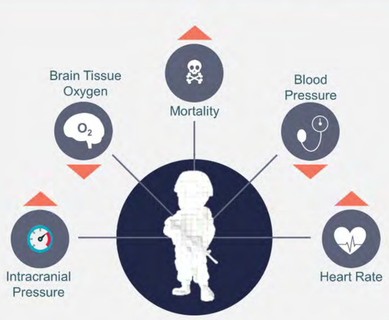
Prophylactic Use of Heparinoids for Deep Vein Thrombosis

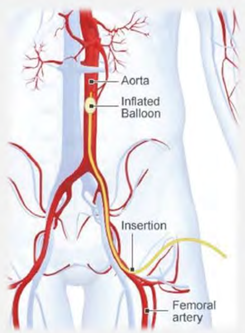




Prehospital Resuscitation Strategies

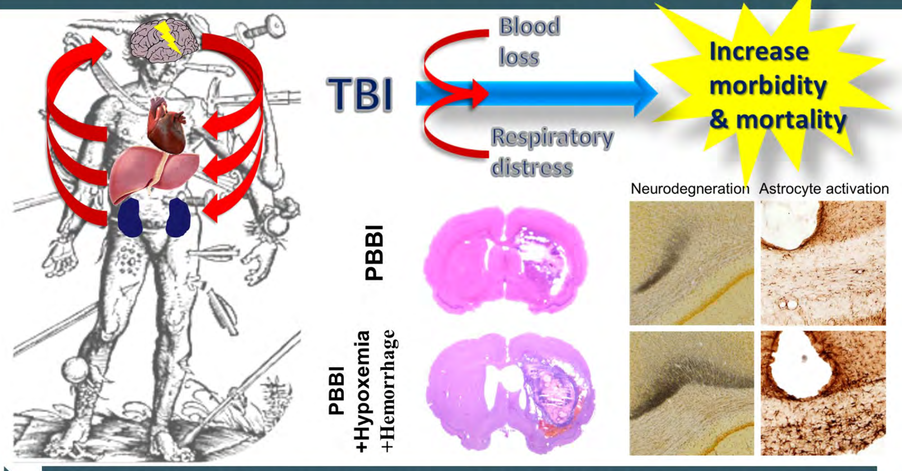
Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) for non-compressible hemorrhage





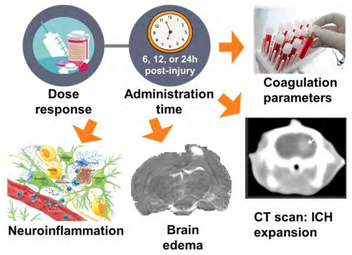
OUR SOLUTIONS

Establish and characterize the animal models of TBI/polytrauma

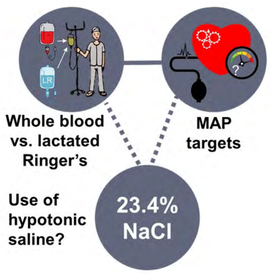


Evaluate clinically relevant physiological/ pathological parameters for each strategy

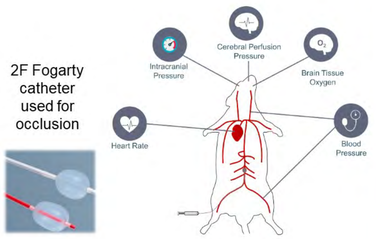
Prophylactic Use of Heparinoids: Evaluating safety and potential neuroprotective effects. Collaboration with CDR Randy Bell, MD, Chief of Neurosurgery (USUHS) and Dr. Anke Scultetus (NMRC).



Prehospital Resuscitation Strategies: Evaluating cerebral edema and physiological changes. Collaboration with Dr. Patrick Kochanek, MD, Director, Safar Center for Resuscitation Research, UPITT Medical School.



REBOA: Evaluating the acute physiological responses to different occlusion paradigms and potential mechanisms of action. Collaboration with Col. Todd Rasmussen, MD Associate Dean of Research at USUHS



ROADMAP TO THE FUTURE

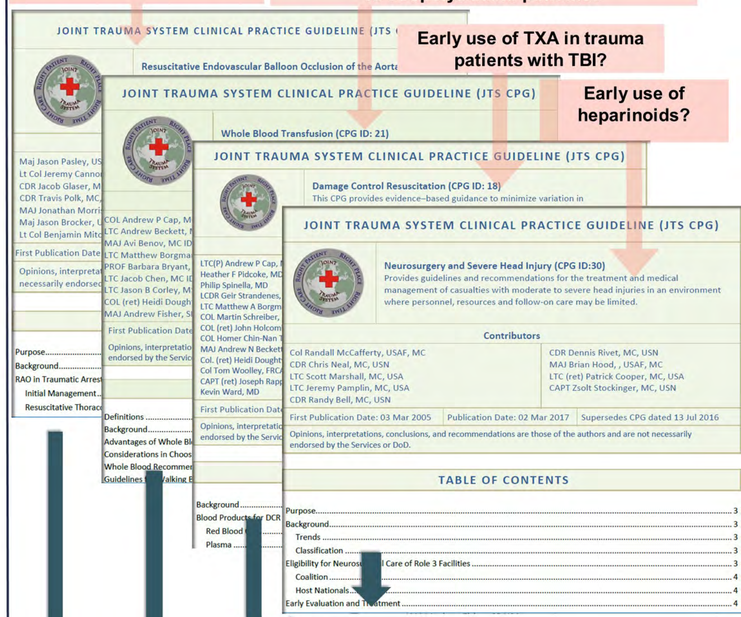
Preclinical data & clinical data → **Level of Evidence**

Prehospital use of REBOA is safe or not safe in patients with hemorrhage and TBI?

Prehospital whole blood transfusion is beneficial to TBI/polytrauma patients?

Early use of TXA in trauma patients with TBI?

Early use of heparinoids?



Funding provided through the Combat Casualty Care Research Program